Review Article
Peroxisome proliferator activated receptor-γ and traumatic brain injury

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Abstract: Traumatic brain injury (TBI) represents a major health care problem and a significant socioeconomic challenge worldwide. No specific therapy for TBI is available. The peroxisome proliferator activated receptor-γ (PPAR-γ) belongs to the nuclear receptor superfamily. Although PPAR-γ was originally characterized in adipose tissue as a regulator of lipid and glucose metabolism, recent studies showed that PPAR-γ is present in most cell types and plays a central role in the regulation of adipogenesis, glucose homeostasis, cellular differentiation, apoptosis and inflammation. Here, we reviewed the current literature on the molecular mechanisms of PPAR-γ-related neuroprotection after TBI. Growing evidence has indicated that the beneficial effects of PPAR-γ activation in TBI appear to be mediated through downregulation of inflammatory responses, reduction of oxidative stress, inhibition of apoptosis, and promotion of neurogenesis. A thorough understanding of the PPAR-γ pathway will be critical to the development of therapeutic interventions for the treatment of patients with TBI.

Introduction

Traumatic brain injury (TBI) represents a major health care problem and a significant socioeconomic challenge worldwide [1-4]. Despite advances in research and improved neurological intensive care in recent years, the clinical outcome of severely head-injured patients is still poor. Survivors of TBI are often left with significant cognitive, behavioral, and communicative disabilities, and some patients develop long-term medical complications [4,5]. The annual economic burden of direct and indirect costs for TBI in the United States alone is estimated at more than $50 billion [6,7]. In its 'World report on traffic injury prevention', the World Health Organization estimates that by 2020, road traffic accidents, which often cause head injury, would be within the top three leading causes of global burden of diseases, surpassing even HIV and tuberculosis. These statistics underline the urgent need for efficient treatment modalities to improve post-traumatic morbidity and mortality.

The damage to the brain after head trauma occurs in two phases: the initial primary phase and an ongoing secondary phase. The initial phase is the injury itself (i.e., immediate mechanical disruption of brain tissue). It is irreversible and amenable only to preventive measures. The secondary phase begins at the time of injury and continues in the ensuing days to weeks. This delayed phase leads to a variety of physiological, cellular, and molecular responses aimed at restoring the homeostasis of the damaged tissue, which, if not controlled, will intensify the damage sustained following TBI. Understanding of the cellular and molecular mechanisms contributing to the development of secondary brain injury after TBI is essential for the identification of new potential therapeutic targets.

Peroxisome proliferator activated receptors

(PPARs) are members of the nuclear receptor superfamily. They can heterodimerize with retinoid X receptor to regulate transcription of genes linked to lipid and glucose metabolism. In 1987, a peroxisome proliferator-binding protein was identified and characterized in the rat liver [8]. The first PPAR was subsequently cloned from the mouse liver [9], followed by other PPAR homologs in other species [10]. Three different PPARs [a,δ (also called β), γ] have been identified [11]. PPAR-γ is the most extensively studied of the three PPAR subtypes to date. PPAR-γ is remarkably conservative across species. Human and murine PPAR-γ proteins show 95% identity at the amino acid level. Human PPAR-γ gene is located on chromosome 3 whereas mouse PPAR-γ gene is located on chromosome 6. Mouse and human PPAR-γ genes reveal a common organization of the translated region in six exons. The genes extend over 100 kb of genomic DNA and generate three mRNA transcripts, PPAR-γ1, PPAR-γ2 and PPAR-γ3, which arise as products of different promoter usage and splicing [12-14]. PPAR-γ1 and PPAR-γ3 mRNAs encode for the same protein, while PPAR-γ2 mRNA gives rise to a protein containing 28 additional amino acids at the N-terminus. Analysis of the tissue distribution of the three mRNA PPAR-γ isoforms revealed some differences. PPAR-γ1 has the broadest tissue expression, while PPAR-γ2 and PPAR-γ3 isoforms are more restrictedly distributed.

PPAR-γ was originally identified as a key regulator of adipocyte differentiation and lipid metabolism [15] and the role of PPAR-γ in regulating glucose homeostasis has also been established [16]. It has been demonstrated that the anti-diabetic drugs known as thiazolidinediones (i.e., rosiglitazone, pioglitazone, troglitazone and ciglitazone) mediate their therapeutic effects through the interaction with PPAR-γ [17]. In addition, several endogenous ligands of PPAR-γ have been identified, including prostaglandin derivatives such as 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2 (15d-PGJ$_2$) [18]. Studies from our laboratory have shown that some non-PPAR-γ ligands such as vasoactive hormone adrenomedullin and its bind protein complex (AM/AMBP-1) [19] and dietary polyphenol curcumin [20,21] can also activate the PPAR-γ pathway. PPAR-γ gene silencing eliminated their beneficial effects ([19] and unpublished data). Recently, a few specific PPAR-γ antago-

nists were also identified. GW9662, a potent irreversible PPAR-γ ligand, is able to block PPAR-γ at 1-10 μM concentrations [22]. LG100641, another PPAR-γ ligand, does not activate PPAR-γ but selectively and competitively blocks thiazolidinediones' activation of the receptor [23]. Although PPAR-g has been investigated for effects of its ligands in modulating lipid metabolism, more and more recent studies have been showing the central role of PPAR-γ in the regulation of adipogenesis [24], glucose homeostasis [25], cellular differentiation [26], apoptosis [27] and inflammation [28,29]. Here, we present a review of the current literature on the molecular mechanisms of PPAR-γ-related neuroprotection after TBI.

PPAR-γ and cerebral inflammation

TBI initiates an acute inflammatory response, which involves the integrated activities of cytokines, chemokines, vascular adhesion molecules, and inflammatory cells [30]. The traumatic injury to brain tissue gives rise to immediate mechanical damage characterized by disruption of cell membranes, cellular organelles, and blood vessels, which causes primary cell death, ischemia, and hemorrhage. These initial events then stimulate resident inflammatory cells in central nervous system (CNS) such as microglia and astrocytes and trigger the release of inflammatory mediators including cytokines, chemokines, neurotransmitters and reactive oxygen radicals or species, which in turn disrupt the blood brain barrier (BBB) and recruit more inflammatory cells [30-32]. These cells then release more inflammatory mediators and exaggerate the inflammatory response. This inflammatory cascade contributes to the acute pathologic processes and long-term neuronal damage following TBI [33].

PPAR-γ plays a major role in the regulation of inflammatory responses [29]. Increasing evidence has shown that PPAR-γ activation mitigates inflammation associated with chronic and acute neurological insults [34-37]. Activation of PPAR-γ in microglia and macrophages can decrease the production of proinflammatory mediators [38,39]. In fact, PPAR-γ induction in microglia and macrophages correlates with decreased microglial and macrophage activation, decreased release of pro-inflammatory mediators and improved neurological outcome [40,41]. Thiazolidinediones have been shown

to be beneficial in several cellular and animal models of CNS diseases where inflammation is a major component of the progressive neurological deficit [41-44]. Interestingly, a recent study has shown that cortical PPAR-γ expression is upregulated after TBI, and administration of PPAR-γ agonists is protective under such a condition [45]. Using a mouse model of TBI induced by controlled cortical impact, Yi et al. [45] showed that PPAR-γ mRNA expression in the cortical tissue surrounding the injury epicenter was more than doubled at 24 h after TBI. Administration of rosiglitazone, a PPAR-γ agonist, further increased PPAR-γ expression, reduced GSI-B4 (a marker of activated microglia/macrophages) and intercellular adhesion molecule-1 (ICAM-1) immunostaining, and downregulated pro-inflammatory cytokine expression in the brain after TBI. Similarly, Hyong et al. [46] showed that rosiglitazone significantly attenuated myeloperoxidase (MPO) activity (a measure of neutrophil infiltration) and decreased tumor necrosis factor-a (TNF-a) and interleukin (IL)-1β expression in a rat model of surgical brain injury.

Several pathways have been associated with PPAR-γ-dependent anti-inflammation [29,47,48]. PPAR-γ can block nuclear factor (NF)-κB-dependent gene expression. Although nuclear receptors repress target genes in the absence of ligands by recruiting corepressors, the molecular mechanism for transcriptional repression by nuclear receptors in response to the binding of ligands remains poorly understood. One possibility involves the reciprocal inhibition of differential transcription systems through limited availability of shared cofactors, sometimes referred to as squelching [29]. PPAR-γ can scavenge transcriptional co-factors, such as steroid receptor co-activator-1 (SRC-1) and cAMP response element-binding protein (CREB) binding protein (CBP/p300). Bound to PPAR-γ, these co-factors are not available for initiating gene expression. Because transcriptional co-factors are indispensable for NF-κB-dependent gene induction, NF-κB-mediated gene expression is downregulated. NF-κB is an important transcription factor involved in pro-inflammatory gene expression. Blocking it can cause a significant attenuation of pro-inflammatory gene expression. A recent report by Glass and colleagues [49] suggests an alternative mechanism, wherein a functionally distinct pool of PPAR-γ is susceptible to ligand-dependent sumoylation at lysine 365, leading to recruitment to and stabilization of the nuclear receptor co-repressor (NCo-R)-histone deacetylase-3 (HDAC3)-transducin beta-like protein 1 (TBL1)-TBLR1 complex at the promoters of pro-inflammatory genes. Thereby, NF-κB-dependent pro-inflammatory gene expression is abolished. Besides inactivating NF-κB, PPAR-γ can also directly associate with other transcription factors such as nuclear factor of activated T cells (NF-AT), activator protein-1 (AP-1), or transducers and activators of transcription (STAT), and block these transcription factors-dependent gene expression [29]. Additionally, PPAR-γ can inhibit phosphorylation of mitogen-activated protein kinase (MAPK), and therefore prevent MAPK-dependent pro-inflammatory gene expression [50].

PPAR-γ and oxidative stress

Oxidative damage is a significant component of the secondary injury cascade following TBI. A massive production of reactive oxygen species is triggered by increased intracellular calcium levels, mitochondrial dysfunction, arachidonic acid breakdown, activation of cyclooxygenase (COX)-2 and inducible nitric oxide synthase (iNOS), and glutamate-mediated excitotoxicity after brain trauma [51,52]. The oxidative cascade begins with the production of superoxide and nitric oxide. These two molecules combine to form peroxynitrite, which leads to the production of multiple damaging free radicals, including nitrogen dioxide, the carbonate radical, and the hydroxyl radical. Together, these free radicals lead to oxidative damage and secondary brain injury [53].

PPAR-γ activation affects the generation of reactive oxygen species on various levels. Systemic and intracerebroventricular administration of thiazolidinedione PPAR-γ agonists reduced the expression of COX-2, an important enzyme involved in the production of reactive oxygen species [54,55]. PPAR-γ agonists also attenuated the expression of iNOS in inflammatory cells [56,57], which is considered to be an important source of the deleterious radical peroxynitrite. On the other hand, PPAR-γ agonists also increase the levels of antioxidants in and around the injured tissue. Pioglitazone has been shown to induce the expression of the antioxidant enzyme superoxide dismutase, which scavenges free oxygen radicals in the injured tissue [58].

Elevated catalase levels were observed in PPAR-γ agonist-treated animals following intracerebral hemorrhage [59]. A recent study has also shown that PPAR-γ agonists reversed the depleted stores of glutathione in the hippocampus in a rat model of stroke [55]. In this regard, PPAR-γ activation may reduce the production of free radicals, and at the same time, elevate enzymes essential for combating free radicals that remain.

PPAR-γ and neural apoptosis

Neuronal apoptosis occurs in naturally physiologic states such as CNS development, as well as pathologic states such as ischemia, viral infection, neurodegenerative diseases, and trauma [60]. Both animal and human studies have shown substantial evidence of neuronal apoptosis after TBI [61]. After a brain insult, the injured tissue usually suffers from two waves of cell death, presumably representing two waves of neuronal death, the first of which is necrotic cell death and the second of which represents a delayed neuronal death by apoptosis. In rat models of TBI, necrosis was suggested to occur in the early post-traumatic period and apoptosis was observed in the chronic post-traumatic period [62]. Decreases in bcl-xl, an inhibitor of apoptosis, and increases in BAX, a promoter of apoptosis, were shown in the rat brain after TBI [63]. TUNEL positive cells were increased after experimental TBI [64,65]. Activation of caspases 3, 7, 9, and 12 was reported in a variety of animal models of TBI [66-68]. In humans, swollen hippocampal neurons in contusions were observed in the early post-traumatic period. These injured neurons eventually shrink and become eosinophilic over time. TUNEL positive cells were observed in histologic samples of TBI patients [69,70]. Caspase 8 was upregulated in the human brain after TBI [71]. Clearly, therapies that protect surrounding cells of the necrotic core, the so-called penumbra, from apoptosis are of great importance, because the loss of these cells contributes to the loss of neurological function and can greatly impact outcome.

PPAR-γ agonists have been shown to increase neuron survival and decrease lesion sizes in animal models of Parkinson's disease [72,73], central inflammation [74], intracerebral hemorrhage [59], and cerebral ischemia [75,76]. In experimental models of TBI, PPAR-γ agonists have also been shown to inhibit neuronal apoptosis. Yi et al. [45] showed that the cortical lesion volume was significantly decreased by rosiglitazone treatment, which was associated with less numbers of TUNEL positive neurons and curtailed induction of caspase 3 and Bax after TBI. These beneficial effects were likely mediated through an indirect mechanism involving the anti-inflammatory and anti-oxidative effects of PPAR-γ. However, PPAR-γ activation may also have a direct anti-apoptotic effect on neurons. Neuronal expression of PPAR-γ has been detected in the intact CNS and an upregulation of PPAR-γ was observed in neurons in the ischemic penumbra following focal cerebral ischemia [75,76]. Using both *in vitro* and *in vivo* models of excitotoxic neuronal injury, Zhao et al. [77] have shown that the endogenous PPAR-γ ligand, 15d-PGJ$_2$, and a selective thiazolidinedione PPAR-γ agonist, ciglitazone, significantly reduced glutamate and NMDA-mediated neuronal death. This neuroprotective effect of 15d-PGJ$_2$ and ciglitazone was linked to increased PPAR-γ DNA binding activity as it was fully reversed by the pretreatment of neurons with selective PPAR-γ antagonists and anti-PPAR-γ antibody.

Interestingly, PPAR-γ agonists have been shown to induce apoptosis in glioma and neuroblastoma cells. In four different glioma cell lines (A172, U87-MG, M059K, M059J), rosiglitazone led to the induction of apoptosis and the PPAR-γ antagonist GW9662 partially reverted these effects [78]. Ciglitazone and 15d-PGJ$_2$ also induced apoptotic cell death in human and rat glioma cells, and apoptotic cell death was correlated with the upregulation of Bax and Bad protein levels [79,80]. In cultured human neuroblastoma cells, 15d-PGJ$_2$ was shown to decrease cellular viability and induce apoptosis [81,82]. The precise mechanisms responsible for differential effects (i.e. pro-apoptotic vs. anti-apoptotic) of PPAR-γ ligands remain incompletely clarified. Certainly, indirect mechanisms such as anti-inflammation and anti-oxidation contribute to the anti-apoptotic effect of PPAR-γ agonists observed in the above mentioned animal models. However, the different effects of PPAR-γ agonists on apoptosis may also be related with the concentrations of PPAR-γ agonists used [83]. Clay et al. [84] have pointed out that modest activation of PPAR-γ results in enhancement of cellular proliferation, whereas vigorous activation might induce apoptosis. Whether

PPAR-γ ligands induce apoptosis or stimulate cell proliferation may depend on the direction of propagation of intracellular signals involved, which reflects the concentration-dependent effect of PPAR-γ ligands on PPAR-γ activation.

PPAR-γ and neurogenesis

During development and throughout our lifetime neuronal death, maintenance and neurogenesis occur in a tightly controlled fashion [85,86]. The neurogenic zones, replete with neural stem cells are found in the subventricular zones, located along the lateral aspects of the lateral ventricles and the subgranular zones, located in the dentate gyrus of the hippocampus. Adult neurogenesis is found in these forebrain regions in all mammalian species examined, including humans [87,88], and may serve to replace cells damaged by brain insults. Normally, the postnatal subventricular zones contributes progenitors to the rostral migratory stream to support ongoing olfactory neurogenesis, while the subgranular zones of the dentate gyrus provides new granular neurons throughout life [89,90]. Following TBI, neural stem cells, supported by their local vasculature, are thought to proliferate, migrate to and differentiate at injury sites, affecting variable degrees of structural and functional recovery [91]. Significant self-recovery occurs following all but the most severe episodes of TBI [92-94]. Although the mechanisms underlying this phenomenon remain largely unknown, it is clear that neural stem cells are activated and increased neurogenesis follows. New neurons are found in the outer layers of the dentate gyrus, where normally this would occur only during early development [95-97]. Injury-induced neurogenesis is one compelling potential contributor to post-injury recovery [91].

PPAR-γ appears to be important in regulating the early brain development and post-injury brain repair [98]. PPAR-γ expression is relatively low in newborn and adult brains. But high levels of PPAR-γ expression were found in embryonic brains [99]. Similarly, neural stem cells isolated from mouse embryos also express high levels of PPAR-γ. Compared with wild-type mice, neural stem cells isolated from heterozygous PPAR-γ-deficient mice exhibited a slower growth rate [100]. Suppression of PPAR-γ protein expression by a lentivirus-mediated short hairpin RNA technique led to a significant reduction in the cell growth rate in neural stem cells [98]. In the case of control infection, which was unable to suppress the expression of PPAR-γ protein, the proliferation of neural stem cells was not altered. Similarly, optimal activation of the PPAR-γ pathway by PPAR-γ agonists stimulated neural stem cell proliferation and inhibited differentiation of neural stem cells into neurons. On the other hand, PPAR-γ antagonists inhibited cell growth and induced apoptosis/death in neural stem cells [100].

Similar to PPAR-γ's effect on apoptosis, PPAR-γ's regulation of neural stem cells is also biphasic. Physiological concentrations of PPAR-γ stimulated neural stem cell growth, whereas excessive activation of PPAR-γ with higher concentrations of agonists resulted in cell death [100]. A recent study has shown that PPAR-γ agonists at concentrations of 100 nM to 3 μM stimulated neural stem cell growth. However, inhibition of cell growth and apoptosis were conversely observed when PPAR-γ agonists' concentrations were above 30 μM [100]. This biphasic effect of PPAR-γ suggests that optimal concentrations of PPAR-γ agonists exist for neurogenesis.

Brain repair/recovery after injury involves both angiogenesis and neurogenesis. PPAR-γ agonists have also been shown to promote angiogenesis in the brain by their action on endothelial progenitor cells [101]. In a rat model of focal cerebral ischemia, Chu et al. [102] have found that rosiglitazone treatment increased the vascular surface area, the vascular branch points, the vascular length, and the number of BrdU (5-bromo-2-deoxyuridine, a marker for dividing cells) positive endothelial cells. Thus, PPAR-γ agonists may also influence brain repair through angiogenesis.

Summary and perspectives

TBI is a major disabling condition all over the world. No specific pharmacological therapy for TBI is available to reduce the incidence of secondary brain injury and adverse outcome. Several pathological events including inflammation, oxidative stress and apoptosis during the acute stage after the injury are known to precipitate the neuronal death and neurological dysfunction. In this review, we highlighted the beneficial effects of PPAR-γ agonists in TBI. The potential molecular mechanisms of PPAR-γ action

were also discussed. The beneficial effects of PPAR-γ agonists in TBI appear to be mediated through the downregulation of inflammatory responses, reduction of oxidative stress, inhibition of apoptosis, and promotion of neurogenesis. However, the exact role of PPAR-γ following TBI remains unclear. And our knowledge of the regulatory mechanisms and signaling cascades underlying the beneficial effects of PPAR-γ in the brain is still limited. Further research in these areas is required. Nevertheless, there is increasing evidence that a thorough understanding of the PPAR-γ pathway will be critical to the development of therapeutic interventions for the treatment of TBI patients.

Acknowledgment

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